Synthesis of Novel Structurally Diverse *N*-Mono- and *N*,*N*′-Disubstituted Benzimidazol-2-one Derivatives by the Alkylations of 1,3-Dihydro-2*H*-benzimidazol-2-one with Some Alkyl Halides under Transfer Catalysis Conditions

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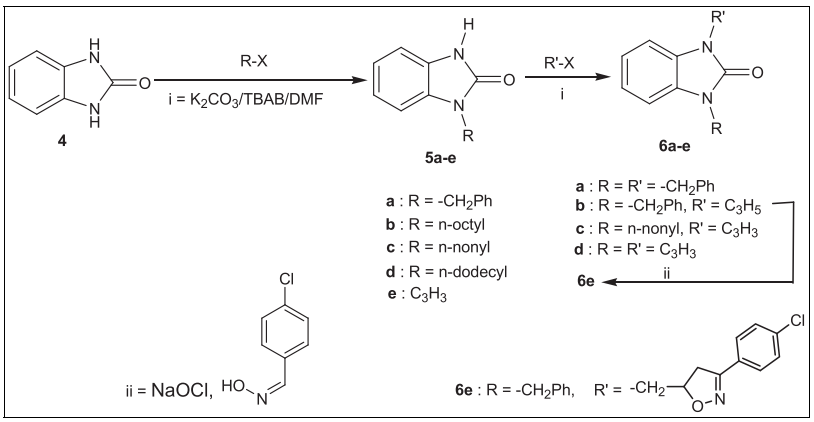


A series of N-mono- and *N*,*N*′-disubstituted benzimidazol-2-one derivatives optionally substituted on both secondary amine functionalities were prepared with excellent yields by reacting 1,3-dihydro-2H-benzimidazol-2-one in one and two steps respectively with various alkyl halides under phase transfer catalytic conditions. One of the synthesized *N*,*N*-disubstituted benzimidazol-2-one derivatives underwent a regiospecific 1,3-dipolar cycloaddition reaction at its side allyl substituent with the *in situ* generated 4-chloro benzonitrile *N*-oxide from 4-chlorobenzaldoxime to afford in good yield the corresponding *N*,*N*′-disubstituted derivative incorporating the 2,5-dihydro-isoxazole nucleus in one of the side chain. All the new compounds were fully characterized by their physical and spectroscopic data.

INTRODUCTION

The chemistry of macrocyclic compounds have attracted much attention during the past few decades, and because of the search for new complexing agents, molecular receptors are able to bind efficiently and selectively charged (ionic) species. Moreover, the high rate at which resistant strains of parasites are developing makes it urgent to search for newer drugs with better therapeutic profile. Among the broad range of templates, benzimidazoles scaffolds represent a class of promising molecules as leading structures for the discovery of novel synthetic drugs. Investigations on the benzimidazole derivatives have led to the findings of new commercial drugs such as Omeprazole [1] and Pimobendan [2]. In particular, drugs incorporating the Benzimidazol-2-one moiety including Domperidone [3–5], Milenperone [6–8], Declenperone [8], Benperidol [8], Neflumozide [9,10], and Benzitramide [11] are widely used.

The development of new synthetic methods of heterocyclic compounds in solution and in solid phase [12] is a fast-growing field of combinatory chemistry.

The benzimidazole nucleus is a substrucrture [13] that can be found in many pharmaceutical agents possessing a large spectrum of biological properties [14]. These include antiviral, anti-ulcerous, antihypertensive, and anticancer agents [12,15–17].

Despite the existence of many methods for the preparation of benzimidazoles [18], there is a real need to designing new synthetic procedures that are simple, reliable, cost effective, and eco-friendly.

In this work, the reactivity of the two nitrogen atoms of benimidazol-2-one toward alkylation with various alkyl halides including benzyle chloride, allyl bromide, n-octyl bromide, n-nonyl bromide, n-dodecyl bromide, and propargyle bromide was investigated under phase transfer catalytic (PTC) conditions. The 1,3-dipolar cycloaddition

reaction of the side allyl substituent of one of the *N*,*N*′-disubstituted benzamidazol-2-one derivatives with 4-chlorobenzaldehyde oxime was equally studied.

RESULTS AND DISCUSSION

Benzimidazolon-2-one substrate used in the alkylating reactions was synthesized by condensing orthophenylenediamine with ethyl chloroformate in refluxing pyridine for 24 h (Scheme 1).

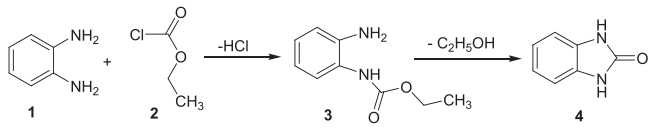
1,3-Dihydro-2H-benzimidazolon-2-one possesses two secondary amine functionalities likely to be alkylated. The classical alkylation techniques require the use of strong bases such as sodium or potassium alcoholates, sodium amide in liquid ammonia or in *N*,*N*-dimethyl formamide. Alternatively, weak bases such as potassium carbonate in acetone can be used [12]. However, these techniques have some drawbacks: They are costly, the reactions are slow, and the reaction products are difficult to purify. To overcome these disadvantages, the alkylation technique under heterogeneous phase transfer catalytic conditions [13] has hitherto been reported to be a more efficient, cost-effective, and environmental friendly alternative.

From a synthetic point of view, this technique has many advantages, namely, the requirement of less energy (reactions proceed at room temperature), the improvement of the yields, and the simpleness of the reactions' logistic. According to the nature of the base, there are two types of phase transfer catalytic conditions: the liquid/liquid and the solid/liquid. In the first case, the base is sodium hydroxide in solution in an aprotic solvent such as dichloromethane, benzene, or toluene. In the second case, a less stronger base such as potassium carbonate is used in solution in DMF, in the presence of a catalyst such as tetra n-butylammonium bromide (TBAB). The salt is insoluble in the organic solvent in which the phase transfer catalyst (TBAB) is dissolved.

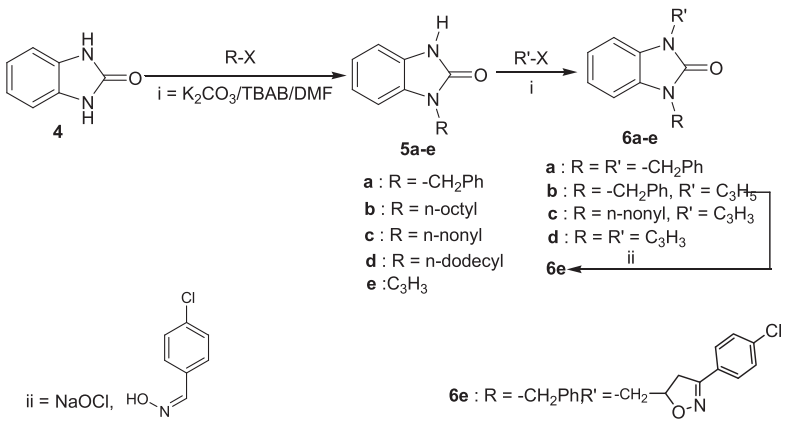
Alkylations with alkyl halides have been extensively investigated in the literature [19,20]. Diversely *N*-alkylated benzimidazol derivatives have been the focus of intensive investigations aiming at generating combinatorial libraries and contributing to the worldwide drug discovery efforts [21–24].

In the light of the previous findings, we reacted compound **4** with benzyle chloride in the heterogeneous liquid–solid phase transfer catalytic conditions, whereby DMF was used as solvent and K_2CO_3 as the base. The crude reaction product obtained consisted of a mixture of the *N*-monobenzylated (**5a**) and *N,N*′-dibenzylated (**6a**) derivatives, which were readily separated by silica gel column chromatography. When subjected to the same alkylating conditions, compound **5a** was successfully converted in to **6a**. All the other diversely alkylated derivatives **5b–e** and **6b–d** (Scheme 2) were respectively prepared by *N*-alkylating compound **4** or the corresponding primarily synthesized precursors **5** with the appropriate alkyl bromide in similar reaction conditions.

Scheme 1. Reactions sequences to 1,3-dihydro-2H-benzimidazolon-2-one (**4**).



Scheme 2. Reactions sequences to the mono-*N*-alkylated benzimidazolone derivatives (**5a–e**) and *N,N*′-dialkylated benzimidazolone derivatives (**6a–e**).



The treatment of compound **6b** with 4-chlorobenzaldoxime in the presence of sodium hypochlorite (NaOCl) gave after the appropriate work-up and purification, a compound to which structure **6e** (Scheme 3) was assigned on the basis of the available spectroscopic data.

The transformation of 4-chlorobenzaldoxime to 4-chloro-benzonitrile *N*-oxide is essentially a dehydrogenation process. Different procedures of this dehydrogenation are thoroughly discussed in the literature [25–29]. It is only necessary to note here that the process is carried out mainly as halogenation dehydrohalogenation. The intermediate hydroximoyl chloride is frequently not isolated (Scheme 3). Two mechanistic alternatives consecutive to the "head-to-head" and the "head-to-tail" interactions between compound **6b** and 4-chloro-benzonitrile *N*-oxide are envisageable. The 1,3-dipolar cycloaddition leading to compound **6e** in which the imine form of the isoxazole nucleus is predominant in comparison with the enamine form is however the most plausible.

The alternative structure **6e'**, which would result from the "head-to-tail" attack, was readily ruled out of consideration on the basis of ^{1}H- and ^{13}C-NMR spectral evidences. In fact, besides the 13 aromatic protons observed around δ_H ppm 7.56 (dd, J = 8.6, J' = 1.2 Hz, 2H), 7.56 (dd, J = 8.6, J' = 1.2 Hz, 2H), 7.30 (m, 5H, aromatic), and 7.07–6.97 (m, 4H, aromatic) because of the three aromatic rings, three groups of multiplets could be found around 5.17–5.13, 4.19–4.15, and 3.44 ppm. They were respectively assigned to the two methylene groups attached to the nitrogen atoms, the methylene of the isoxazole ring, and the hydrogen atom carried by the tertiary carbon atom of the isoxazole ring. The corresponding signals of the previous carbons were found in the ^{13}C-NMR spectrum and readily assigned. These spectral evidences clearly confirmed the regioselectivity of the previous 1,3-dipolar cycloaddition mechanism (Scheme 3). The structures of all the new compounds were assigned on the basis of the available physical and spectroscopic data.

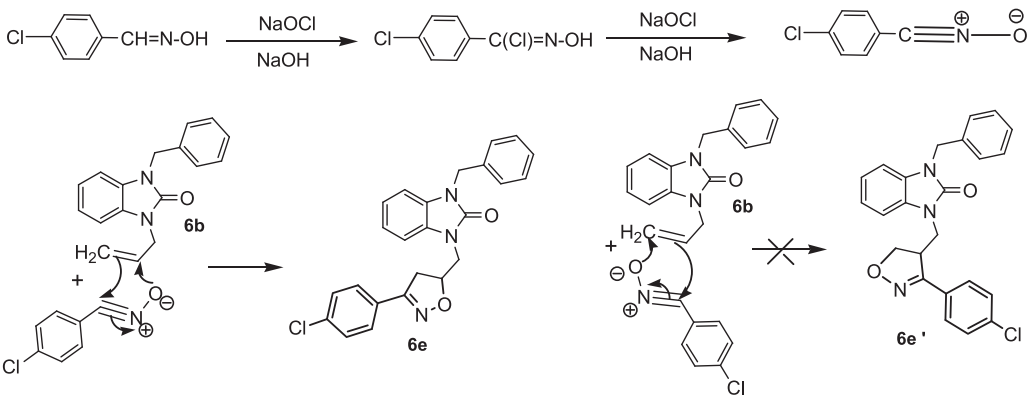
EXPERIMENTAL

Uncorrected melting points were measured with a Buchi apparatus. The NMR spectra where recorded on a Brucker AC300- instrument. The chemical shifts are given in parts per million (ppm) with reference to tetramethylsilane (TMS) used as internal reference, with a precision of ±0.1 for the ^{13}C-NMR and ± 0.05 for the ^{1}H-NMR. The mass spectra were recorded on a Nermag R10-10C instrument.

1,3-Dihydro-2H-benzimidazol-2-one (4). In a two-necked round-bottom flask fitted with a dropping cylinder (containing ethyl chloroformate) was dissolved 4 g (0.037 mol) of *o*-phenylenediamine (**1**) in pyridine (30 mL). To the vigorously stirred and ice-cooled (0°C) solution was added dropwise 1.2 g (4.123 mL) of ethyl chloroformate over a 20-min period, and the reaction mixture was refluxed for 24 h. The solvent was then evaporated to dryness under reduced pressure, and the resulted residue was purified by silica gel column chromatography using ethyl acetate/petroleum ether (1:2) as eluent to afford a product that was crystallized from dichloromethane to give 3.32 g (83%) of compound **4** as white crystals; mp: 300–302°C; Rf: 0.46 from Petroleum ether/ethyl acetate (2:1); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.92 (m, 4H), 10.2 (s, 2H); IR (KBr): ν_{max} 3016, 1755, 1629, 1483 cm^{-1}; ^{13}C NMR ($CDCl_3$, 100 MHz): δ121, 124.6, 129.9, 155.2; ESI-MS: *m/z* (rel. abund.%) 135.2 (M^+, 100).

Preparation of compounds 5a and 6a. In a two-necked round-bottom flask fitted with a dropping cylinder (containing benzyl bromide) was dissolved 1.2 g (0.34 mol) of benzimidazolone **4**, 1.47 g (0.01 mol) of K_2CO_3 in DMF (30 mL). The mixture was stirred over 5 min after what, 0.01 g of TBAB was added and 1.36 g of benzyl bromide was subsequently added dropwise to the vigorously magnetic stirred mixture. The mixture was then further stirred at room temperature for 24 h. The precipitating salts were filtered, and the DMF was evaporated under reduced pressure to afford a residue that was dissolved in dichloromethane, washed three times

Scheme 3. *In situ* generation of 4-chloro-benzonitrile *N*-oxide and the two mechanistic alternatives of its 1,3-dipolar cycloaddition with compound **6b**.



with distilled water to remove all traces of salts. The combined organic fractions were dried with Na_2SO_4. After filtration, dichloromethane was evaporated and the resulted crude material consisting of two different substances (analytical TLC) was purified by silica gel column chromatography using ethyl acetate/hexane (1:2) as eluent to afford two different crude products that were crystallized from dichloromethane to give respectively 0.8 g (67%) of compound **6a** as white crystals and 0.372 g (31%) of compound **5a** as white crystals. Compound **5a** could be subsequently alkylated to compound **6a** by applying the same protocol.

1-Benzyl-1,3-dihydro-2H-benzimidazol-2-one (5a). mp: 197–200°C; Rf: 0.442 from hexane/ethyl acetate (2:1); IR: ν_{max} cm^{-1} (KBr) 3043, 2946, 1705, 1494, 1435, 1398, 1246, 1121, 1003, 731; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ_H ppm = 7.34–7.29 (m, 4H), 7.27–7.25 (m, 1H), 7.09–7.06 (m, 1H), 7.02–6.97 (m, 2H), 6.87 (d, J = 7.5 Hz, 1H), 5.08 (s, 2H). ^{13}C-NMR ($CDCl_3$, 125 MHz): δ_C ppm = 154.7, 136.5, 130.2, 129.3, 128.8, 127.8, 127.6, 121.4, 121.3, 108.3, 107.5, 45.0. ESI-MS: *m/z* (rel. abund.%) 225 (100).

1,3-Dibenzyl-1,3-dihydro-2H-benzimidazol-2-one (6a). mp: 166–168°C; Rf: 0.785 from hexane/ethyl acetate (2:1); IR (KBr): ν_{max} cm^{-1} 3025, 2926, 1691, 1489, 1436, 1407, 1356, 1164, 750, 696, 659; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H ppm 7.41–7.26 (m, 10H, Ar-H); 7.01–6.97 (m, 2H, Ar-H); 6.95–6.90 (m, 2H, Ar-H); 5.15–5.4 (s, 4H, CH_2). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ_C ppm 154.68 (C=O); 136.39, 129.27 (quaternary C-atoms); 128.85, 127.54, 121.57, 108.53 (arom. CH). 45.01 (CH_2). ESI-MS: *m/z* (rel. abund.%) 315 (100).

1-Octyl-1,3-dihydro-2H-benzimidazol-2-one (5b). In a two-necked round-bottom flask fitted with a dropping cylinder (containing octan-1-yl bromide) was dissolved 0.2 g (0.0015 mol) of benzimidazolone **4**, 0.25 g (1.2 equivalent) of K_2CO_3 in DMF (20 mL). The mixture was stirred over 5 min after what, 0.001 g of TBAB was added and 0.53 g (0.9 equivalent) of octan-1-yl bromide was subsequently added dropwise to the vigorously magnetic stirred mixture. The mixture was then further stirred at ambient temperature for 12 h. The precipitating salts were filtered, and the DMF was evaporated under reduced pressure to afford a residue that was dissolved in dichloromethane, washed three times with distilled water to remove all traces of salts. The combined organic fractions were dried with Na_2SO_4. After filtration, dichloromethane was evaporated and the resulted crude material was purified by silica gel column chromatography using ethyl acetate/petroleum ether (1:2) as eluent to afford a crude product that was crystallized from dichloromethane to give (0.134 g, 67%) of compound **5b** as white crystals. mp: 280°C; Rf: 0.57 from petroleum ether/ethyl acetate (2:1); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H ppm 10.61 (1H, s, NH); 7.28–7.00 (4H, m, Ar-H); 3.91(2H, t, J = 7.5 Hz, CH_2); 1.84–1.75 (2H, m, CH_2); 1.43–1.28 (10H, m, CH_2); 0.88 (3H, t, J = 6.3 Hz, CH_3). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ_C ppm 155.93 (C=O); 130.36, 128.18 (quaternary C-atoms); 121.34, 121.10, 109.79, 107.85 (arom. CH); 40.92, 31.78, 29.27, 29.18, 28.44, 26.88, 22.61 (CH_2); 14.06(CH_3). ESI-MS: *m/z* (rel. abund.%) 434 (100).

1-Nonyl-1,3-dihydro-2H-benzimidazol-2-one (5c). In a two-necked round-bottom flask fitted with a dropping cylinder (containing nonan-1-yl bromide) was dissolved 1.2 g (0.09 mol) of benzimidazolone **4**, 2.47 g of K_2CO_3 in DMF (20 mL). The mixture was stirred over 5 min after what, 0.001 g of TBAB was added and 2 g (3 equivalents) of nonan-1-yl bromide was subsequently added dropwise to the vigorously magnetic stirred mixture. The mixture was then further stirred at ambient temperature for 12 h. The precipitating salts were filtered, and the DMF was evaporated under reduced pressure to afford a residue that was dissolved in dichloromethane, washed three times with distilled water to remove all traces of salts. The combined organic fractions were dried with Na_2SO_4. After filtration, dichloromethane was evaporated and the resulted crude material was purified by silica gel column chromatography using ethyl acetate/petroleum ether (1:2) as eluent to afford a crude product that was crystallized from dichloromethane to give (0.852 g, 71%) of compound **5c** as white crystals. mp: 180–182°C; Rf: 0.31 from petroleum ether/ethyl acetate (2:1); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H ppm 10.54 (1H, s, NH), 7.28–7.00 (4H, m, Ar-H); 3.91 (2H, t, J = 7.2 Hz, CH_2); 1.82–1.71 (2H, m, CH_2); 1.50–1.00 (12H, m, CH_2); 0.90 (t, 3H, J = 4.5 Hz, CH_3). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ_C ppm 155.89 (C=O); 130.36, 128.16 (quaternary C-atoms); 130.90, 128.84, 109.77, 107.85 (Arom. CH); 65.57 (CH_2); 40.92, 31.83, 30.58, 29.47, 29.31, 29.23, 28.44, 26.88, 22.64, 19.19 (CH_2); 14.08 (CH_3). ESI-MS: *m/z* (rel. abund.%) 260 (100).

1-Dodecyl-1,3-dihydro-2H-benzimidazol-2-one (5d). In a two-necked round-bottom flask fitted with a dropping cylinder (containing dodecan-1-yl bromide) was dissolved 0.2 g (0.0015 mol) of benzimidazolone **4**, 0.27 g (1.2 equivalent) of K_2CO_3 in DMF (20 mL). The mixture was stirred over 5 min after what, 0.01 g of TBAB was added and 0.31 mL (0.46 g, 0.9 equivalent) of dodecan-1-yl bromide was subsequently added dropwise to the vigorously magnetic stirred mixture. The mixture was then further stirred at ambient temperature for 12 h. The precipitating salts were filtered, and the DMF was evaporated under reduced pressure to afford a residue that was dissolved in dichloromethane, washed three times with distilled water to remove all traces of salts. The combined organic fractions were dried with Na_2SO_4. After filtration, dichloromethane was evaporated and the resulted crude material was purified by silica gel

column chromatography using ethyl acetate/petroleum ether (1:2) as eluent to afford a crude product that was crystallized from dichloromethane to give 0.118 g (59%) of compound **5d** as white crystals. mp: 280°C; Rf: 0.67 from petroleum ether/ethyl acetate (2:1); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H ppm 10.39 (1H, s, NH); 7.28–7.00 (4H, m, Ar-H); 3.90 (2H, t, J = 7.5 Hz, CH_2); 1.84–1.74 (2H, m, CH_2); 1.37–1.26 (18H, m, CH_2); 0.89 (3H, t, J = 6.3 Hz, CH_3). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ_C ppm 155.82 (C=O); 130.36, 128.11 (quaternary C-atoms), 121.35, 121.14, 109.75, 107.87 (Arom. CH); 40.94, 31.91, 29.62, 29.61, 29.58, 29.51, 29.33, 29.31, 28.44, 26.88, 22.68 (CH_2); 14.11 (CH_3). ESI-MS: *m*/*z* (rel. abund.%) 434 (100).

1-Benzyl-3-(prop-2-en-1-yl)-1,3-dihydro-2H-benzimidazol-2-one (6b). In a two-necked round-bottom flask fitted with a dropping cylinder (containing allyl bromide) was dissolved (0.487 g, 0.0021 mol) of 1-benzyl-1H-benzo [d]imidazol-2(3H)-one (**5a**), 0.58 g (1.2 equivalent) of K_2CO_3 in DMF (20 mL). The mixture was stirred over 5 min after what, 0.07 g of TBAB was added and 0.22 mL (two equivalents) of allyl bromide was subsequently added dropwise to the vigorously magnetic stirred mixture. The mixture was then heated to reflux for 48 h. The precipitating salts were filtered, and the DMF was evaporated under reduced pressure to afford a residue that was dissolved in dichloromethane, washed three times with distilled water to remove all traces of salts. The combined organic fractions were and dried with Na_2SO_4. After filtration, dichloromethane was evaporated and the resulted crude material was purified by silica gel column chromatography using ethyl acetate/hexane (1:2) as eluent to afford a crude product that was crystallized from dichloromethane to give compound **6b** as white crystals. mp: 150–151°C; Rf: 0.42; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H ppm 7.33–7.25 (m, 5H, Ar-H); 7.07–6.87 (m, Ar-H); 5.95 (m, 1H, CH=C), 5.27 (m, CH_2 = C); 5.1 (S, -CH_2-N); 4.65–4.58 (dt, N-$\underline{CH_2}$-CH). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ_C ppm 171.098 (C=O); 136.29, (Cq Ar-$\underline{C}$-CH_2-), 132.01 (C=$\underline{CH}$-N), 129.35–129.21 (C-N), 129.2–127.45 (Ar-CH); 117.59 (=CH_2), 65.228 (N-CH_2-); 29.62, 29.61, 29.58, 29.51, 29.33, 29.31, 28.44, 26.88, 22.68 (-CH_2-); 14.11 (CH_3). ESI-MS: *m*/*z* (rel. abund.%) 264(100).

1-Nonyl-3-(prop-2-yn-1-yl)-1,3-dihydro-2H-benzimidazol-2-one (6c). In a two-necked round-bottom flask fitted with a dropping cylinder (containing propargyl bromide) was dissolved (0.21 g, 0.0015 mol) of compound **5c**, 0.28 g (1.2 equivalent) of K_2CO_3 in DMF (20 mL). The mixture was stirred over 5 min after what, 0.072 g of TBAB was added and 0.15 mL (two equivalent) of propargyl bromide was subsequently added dropwise to the vigorously magnetic stirred mixture. The mixture was then further stirred at ambient temperature for 6 h. The precipitating salts were filtered, and the DMF was evaporated under reduced pressure to afford a residue that was dissolved in dichloromethane, washed three times with distilled water to remove all traces of salts. The combined organic fractions were dried with Na_2SO_4. After filtration, dichloromethane was evaporated and the resulted crude material was purified by silica gel column chromatography using ethyl acetate/hexane (1:2) as eluent to afford a crude product that was crystallized from dichloromethane to give (0.176 g, (84%) of compound **6c** as white crystals. mp: 205–207°C; Rf: 0.67 petroleum ether/ethyl acetate (2:1); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H ppm 7.20–6.99 (m,4H, Ar-H); 4.69 (2H, d, J = 2.7 Hz, CH_2); 3.88 (2H, m, CH_2); 2.30 (1H, t, J = 2.4 Hz, ≡CH); 1.80–1.70 (2H, m, CH_2); 1.34–1.26 (12H, m, CH_2); 0.88 (3H, t, J = 6.3 Hz, CH_3). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ_C ppm 155–169 (C = 0); 130.39, 129.55, 128.45, 128.22 (quaternary C-atoms); 130.88, 128.83, 121.61, 121.26, 121.17, 121.04, 109.69, 108.41, 107.79 (Arom.CH) 72.65, 65.53, 41.37, 40.87, 31.82, 30.42, 29.46, 29.42, 29.30, 29.27, 29.22, 28.43, 28.39, 26.86 (-CH_2-); 26.84 (CH_3). ESI-MS: *m*/*z* (rel. abund.%) 298(100).

1,3-Di(prop-2-yn-1-yl)-1,3-dihydro-2H-benzimidazol-2-one (6d). In a two-necked round-bottom flask fitted with a dropping cylinder (containing propargyl bromide) was dissolved 0.4 g (0.003 mol) of benzimidazolone **4**, 0.37 g (2.4 equivalent) of K_2CO_3 in DMF (20 mL). The mixture was stirred over 5 min after what, 0.072 g (0.2 equivalent) of TBAB was added and 0.2 mL (2 equivalents) of propargyl bromide was subsequently added dropwise to the vigorously magnetic stirred mixture. The mixture was then further stirred and heated to reflux for 48 h. The precipitating salts were filtered, and the DMF was evaporated under reduced pressure to afford a residue that was dissolved in dichloromethane, washed three times with distilled water to remove all traces of salts. The combined organic fractions were dried with Na_2SO_4. After filtration, dichloromethane was evaporated and the resulted crude material was purified by silica gel column chromatography using ethyl acetate/hexane (1:2) as eluent to afford a crude product that was crystallized from dichloromethane to give (0.244 g and 61% of compound 6d as white crystals; mp: 121–123°C; Rf: 0.41from petroleum ether/ethyl acetate (2:1); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H ppm 7.28–7.16 (4H, m, Ar-H); 4.7 (S, CH_2-N); 2.31 (S, ≡CH). ESI-MS: *m*/*z* (rel. abund.%) 210 (100).

1-Benzyl-3-[3-(4-chlorophenyl)-4,5-dihydro-1,2-oxazol-5-yl]-1,3-dihydro-2H-benzimidazol-2-one (6e). In a two-necked round-bottom flask fitted with a dropping cylinder (containing 7.5 mL NaOCl) were dissolved (0.48 g, 00018 mol) of compound **6b** and 0.35 g (1.2 equivalent) of 4-chlorobenzaldoxime in 160 mL of chloroform. The

mixture was cooled to −5 to 0°C in an ice-NaCl bath. To the mixture was added dropwise under vigorous magnetic stirring 7.5 mL of NaOCl. The reaction was carried out for 5 h. The resulted mixture was extracted with dichloromethane, and the organic layer was dried with Na_2SO_4. After removing the solvent by evaporation under reduced pressure, the crude product was purified by silica gel column chromatography using hexane/ethyl acetate (2:1) as eluent to afford a white powder that was crystallized from dichloromethane to give (0.259 g, 54%) of compound **6e** as white crystals. mp: 144–146°C; Rf: 0.72 (ethyl acetate/hexane 1:2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H ppm 7.57–7.55 (dd, J = 8.6, J' = 1.2, 2H), 7.54–7.52 (dd, J = 8.6, J' = 1.2, 2H), 7.35–7.25 (m, 5H, aromatic), 7.07–6.87 (m, 4H, aromatic), 5.17 (broad singlet, 1H, NH,), 5.13 (s, 1H), 4.19 (S, 2H, -CH_2-N), 4.15 (S, 2H, -CH_2-N), 3.44 (s, 2H, -CH_2-). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ_C ppm 171.098 (C=O); 155 (C-Cl); 136.29 (Cq Ar-C-CH_2), 132.01(C=CH-N), 129.35–129.21 (C-N), 129.2–127.45 (arom-CH); 117.59 (arom-CH), 65.228 (N-CH_2-), 62.228 (N-CH_2-), 61.228, 29.62, 29.58, 29.51, 29.33, 29.31, 28.44, 26.88, 22.68 (-CH_2-). ESI-MS: *m*/*z* (rel. abund.%) 417(100).

CONCLUSIONS

In summary, a simple, efficient, selective, and eco-friendly method for the preparation of diversely substituted mono-*N*- and *N*,*N*′-dialkylated benzimidazolone derivatives from 1,3-dihydro-2H-benzimidazolon-2-one and various alkyl halides under phase transfer catalysis was reported. Further studies are on-going with the aim to establish a more rational and generalizable protocol for the alkylation of the secondary amine functionalities of 1,3-dihydro-2H-benzimidazolon-2-one under PTC. Investigations toward the construction of hybrid polycyclic molecular architectures incorporating isoxazole or other potential heteroaromatic pharmacophores from substrate **4** are on the way.

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REFERENCES AND NOTES

[1] Melnichouk, S.; Friendship, R. M.; Dewey, C. E.; Bildfell, R. Can J Vet Res 1999, 63, 248.

[2] Hirofumi, O.; Makoto, K.; Akiko, S.; Yasuhiro, I.; Fumitaka, I.; Tsutomu, M. A. O.; Naoya, M.; Kiyoyuki, O.; Hiromi, S.; Akira, K.; Hiroshi, I.; Kazuo, A. Bioorg Med Chem Lett 2008, 18, 3310.

[3] Shobhit, S.; Pandeya, S. N.; Meena, K. Y.; Singh, B. K. J Chem 2013 1.

[4] Kennis, L. E. L.; Vandenberk, J.; Boey, J. M.; Mertens, J. C.; van Heertum, A. H. M.; Janssen, M.; Awouters, F. Drug Dev Res 1986, 8, 133.

[5] Calvo, M. F. Chem Abstr 1986, 106, 67314.

[6] De Cuyper, H.; van Praag, H. M.; Verstraeten, D. Neuropsychobiology 1985, 13, 1.

[7] Gelders, Y. G.; Reyntjens, A. J.; Aerts, T. J ActaPsychiatricaBelgica 1984, 84, 151.

[8] Megens, A. A. H. P.; Kennis, L. E. J Prog Med Chem 1996, 33, 185.

[9] Junggrenand, U. K.; Sjostrand, S. E. Eur Pat Appl 1979, 5, 129 *via* Chem. Abstr. 1979, 92: 198,392z.

[10] Davis, L.; Klein, J. T. U.S. Patent 1983, 4,390,544; *via* Chem. Abstr. 1983, 99: 122,458r.

[11] Knape, H. Br J Anaesth 1970, 42, 325.

[12] Gravatt, G. L.; Baguley, B. C.; Wilson, W. R.; Denny, W. A. J Med Chem 1994, 37, 4338.

[13] Lindberg, P.; Nordberg, P.; Alminger, T.; Braendstroem, A.; Wallmark, B. J Med Chem 1986, 29, 1327.

[14] Khan, A. T.; Mondal, E.; Ghosh, S.; Islam, S. Eur J Org Chem 2004, 2004, 2002.

[15] Kim, J. S.; Gatto, B.; Yu, C.; Liu, A.; Liu, L. F.; LaVoie, E. J. J Med Chem 1996, 39, 992.

[16] Roth, T.; Morningstar, M. L.; Boyer, P. L.; Hughes, S. H.; Buckheit, R. W. Jr.; Michejda, C. J. J Med Chem 1997, 40, 4199.

[17] Horton, D. A.; Bourne, G. T.; Smythe, M. L. Chem Rev 2003, 103, 893.

[18] Cheng, C. C.; Shipps, G. W. Jr.; Yang, Z.; Sun, B.; Kawahata, N.; Soucy, K. A.; Soriano, A.; Orth, P.; Xiao, L.; Mann, P.; Black, T. Bioorg Med Chem Lett 2009, 19, 6507.

[19] Salvatore, R. N.; Yoon, C. H.; Woon, K. Tetrahedron 2001, 57, 7785.

[20] Adimurthy, S.; Joshi, G. Indian J Chem 2010, 49B, 771.

[21] Ding, K.; Wang, A.; Boerneke, M. A.; Dibrov, S. M.; Hermann, T. Bioorg Med Chem Lett 2014, 24, 3113.

[22] Srestha, N.; Banerjee, J.; Srivastava, S. IOSR J Pharm 2014, 4, 28.

[23] Sullivan, J. D.; Giles, R. L.; Looper, R. E. Curr Bioact Compd 2009, 5, 1.

[24] Allschwil, S. H.; Reinach, E. R.; Som, J. United States Patent 4,138,568, Feb 6, 1979.

[25] Carlucci, L.; Liani, G.; Proserpio, D. M.; Rizzato, S. New J Chem 2003, 27, 483.

[26] Kantouch, A.; Abdel-Fattah, S. H. Chem Zvesti 1971, 25, 222.

[27] Bijudas, K.; Bashpa, P.; Bibin, V. P.; Nair, L.; Priya, A. P.; Aswathy, M.; Krishnendu, C.; Lisha, P. Bull Chem React Eng Catal 2015, 10, 38.

[28] Azizi, M.; Biard, P.-F.; Couvert, A.; Benamor, M. Chem Eng Res Des 2014, 94, 141.

[29] Amin, G. C.; Wadekar, S. D. Indian J Text Res 1977, 3, 20.

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